Cryptococcus neoformans var grubii meningoencephalitis in a patient on fingolimod for relapsing-remitting multiple sclerosis: case report and review of published cases

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Introduction

- Fingolimod is a sphingosine-1-phosphate (S1PR) modulator used in the treatment of relapsing-remitting multiple sclerosis (RRMS)
- Fingolimod leads to the sequestration of naïve and memory T cells in secondary lymphoid organs, and prevention of their infiltration into the central nervous system
- Several cases of invasive cryptococcosis have been described in patients on Fingolimod therapy

Aim

- To describe a case of Cryptococcal meningoencephalitis attributable to *Cryptococcus neoformans var. grubii* in the context of long-term fingolimod for RRMS
- To compare and contrast this with previous cases in the literature

Case Summary

- A 58-year-old man, presented to an Australian teaching hospital with fever and confusion, preceded by two weeks of headache.
- He was diagnosed with RRMS 18 years prior, on oral fingolimod (500 microg daily) for 7 years.
- Routine monitoring demonstrated a persistent lymphopenia (range 0.3–0.6 x10^9/L) following commencement of Fingolimod.
- He lived alone with several pet budgerigars.
- On examination he was febrile (38.3°C), but with otherwise normal vital signs. Neurological examination confirmed abnormal mentation with disorientation and inappropriate behaviour. Right-sided lower limb hypertonia and extensor plantar response were longstanding. Further examination was unremarkable.
- Preliminary investigations revealed a mild lymphopaenia [0.9 x10^9/L (ref 1.0–4.0), monocytes 0.7 x10^9/L (ref 0.0–1.0)], and negative HIV serology. Electrolytes and other blood counts were normal.
- MRI brain demonstrated signs of early cerebritis involving the cerebral vertex of bilateral parietal lobes with mild sulcal effacement and leptomeningeal enhancement.
- Diagnostic and therapeutic LP results are demonstrated in **Table 1**, confirming a diagnosis of *C. neoformans* menigioencephalitis
- Serum Cryptococcal antigen titre was 1:2560 at diagnosis.
- Induction therapy with conventional amphotericin B (1 mg/kg daily) and 5-flucytosine (25 mg/kg 6-hourly), for 14 days given early culture conversion.
- After 8-weeks' consolidation therapy with fluconazole 400mg BD, he transitioned to maintenance fluconazole 400mg OD.

Table 2. Published cases of cryptococcal infection in patients taking fingolimod for multiple sclerosis (MS)

Year	Age/ Sex	Country	Duration of Fingolimod	Species	Infection Site	Lym (/µL)	CD4 Count (/µL)	Ref
2020	63M	USA	7 years	SNI	Skin	ND	13	1
2020	34M	USA	5 years	grubii	Disseminated (CNS, blood)	ND	61	2
2020	49F	Germany	5.5 years	grubii	Disseminated (CNS, blood)	90	74	3
2019	**58M**	**Australia**	**7 years**	**grubii**	**CNS**	**300–900**	**ND**	**4** ◀
2019	45M	USA	3 years	neoformans	Lung	680	ND	*
2019	40F	USA	2 years + 3 months	neoformans	CNS	200	ND	*
2017	61F	USA	4 years + 10 months	neoformans	CNS	321	69	*
2017	61F	Australia	3 years	SNI	CNS	120	5	*
2017	47M	USA	2 years	neoformans	Skin	300	73	*
2016	67F	USA	3 years + 5 months	neoformans	CNS	60 – 800	ND	*
2016	63M	Japan	2 years	neoformans	Disseminated (CNS, skin & lung)	300	145	*
2016	62M	USA	3 years	neoformans	CNS	330	ND	*
2016	62F	USA	3 years	neoformans	Skin	650	56	*
2015	50M	USA	3 years + 6 months	SNI	Disseminated (CNS, skin)	500	ND	*
2015	40M	Switzerland	2 years	SNI	CNS	400	56	*
2014	ND	ND	ND	SNI	Lung	ND	ND	*

Legend: CNS = central nervous system; Lym = lymphocyte count; ND = not described; SNI = species not identified ◀ Denotes our case * **References in published report**

Discussion

- *C. neoformans* is an encapsulated, saprophytic yeast concentrated in avian excrement.
- Cryptococcal infection in patients receiving fingolimod is an emerging clinical niche for cryptococcosis
- Herpes virus infections, lower respiratory tract infections, progressive multifocal leukoencephalopathy previously reported in Phase III Fingolimod trials
- 16 published cases of invasive cryptococcosis in the context of fingolimod therapy **(Table 2).**
- Patients all HIV negative and prescribed fingolimod for between 2 and 7 years.
- 11 patients (69%) had cryptococcal meningoencephalitis, 3 (19%) had pulmonary and 4 (25%) had cutaneous infection.
- 10 patients had documented cessation of fingolimod in addition to directed antifungal therapy. All patients with disseminated or CNS diseases received induction therapy containing amphotericin.
- 3 patients had a documented resurgence of symptoms after withdrawal of fingolimod therapy, attributable to immune reconstitution inflammatory syndrome or disease relapse. Of patients with CNS infection, 3 (27%) survived with associated additional disability, while two patients (18%) died.
- All patients presented with varying degrees of peripheral lymphopenia. 8 patients in whom a CD4 count was performed reported a CD4 count of less than 100 cells/microL.

Issues:

- Optimal strategies for prevention of this infection for high-risk groups remain unclear.
- Most cases appear to occur in the first 2–4 years of fingolimod therapy, and are often associated with significant morbidity
- Unclear role of monitoring for lymphopenia or CD4 count to help identify those most at risk and role fluconazole prophylaxis.
- All patients prescribed fingolimod should be educated about the risk of cryptococcosis, the avoidance of environmental risk factors and symptoms of meningitis as a minimum.

Table 1. Cerebrospinal fluid (CSF) analysis by days after commencing antifungal treatment.

	Day 0	Day 1	Day 5	Day 14	Day 20
Opening pressure (cm H_2O)	–	29	14	23	20.5
Appearance	Clear	Clear	Clear	Clear	Clear
Glucose (2.0–3.9 mmol/L)	2.2	–	2.1	2.9	3.3
Protein (0.15–0.45 g/L)	1.01	–	1.35	0.99	0.95
Erythrocytes (x10^6/L)	34	–	181	25	64
Leukocytes (x10^6/L)	62	–	179	88	31
- Polymorphs	0	–	2	0	0
- Monocytes	62	–	177	88	31
Gram stain	Yeasts ++	–	Yeasts +	–ve	–ve
Culture	Cn	–	No growth	No growth	No growth

Legend: + light, ++ moderate, +++ heavy.
Cn = *C. neoformans var grubii*

Outcome

- Delirium rapidly resolved, and he experienced a gradual resolution of headache on treatment.
- He was discharged home after a 20-day admission.
- The patient gave his budgerigars away
- He was subsequently commenced on fortnightly peginterferon beta-1a after 21 weeks of antifungal therapy.

References

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